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UNIVERSITY OF TORONTO MEDICAL JOURNAL

Editorial		2
Preceptor and Student	Ralph F. Hull, 5T9	3
Aldosterone	R. H. Curry, 5T9	5
Clinical Applications of Free Tissue Transplants	D. R. Wilson, 5T9	17
Nausea and Vomiting: Mechanism and Treatment	Reva Moscarello, B.A., 5T9, Harry Schachter, B.A., 5T9	26

NOVEMBER 1958

VOLUME XXXVI NUMBER 1

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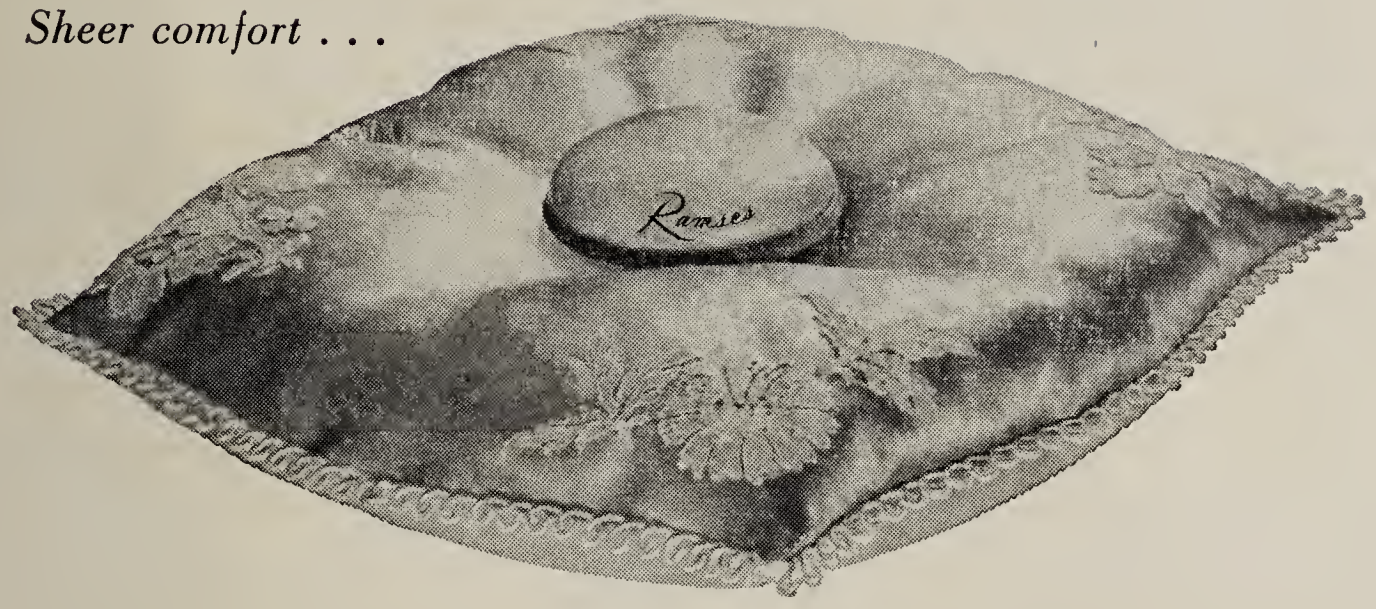

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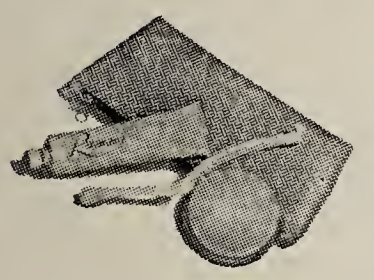

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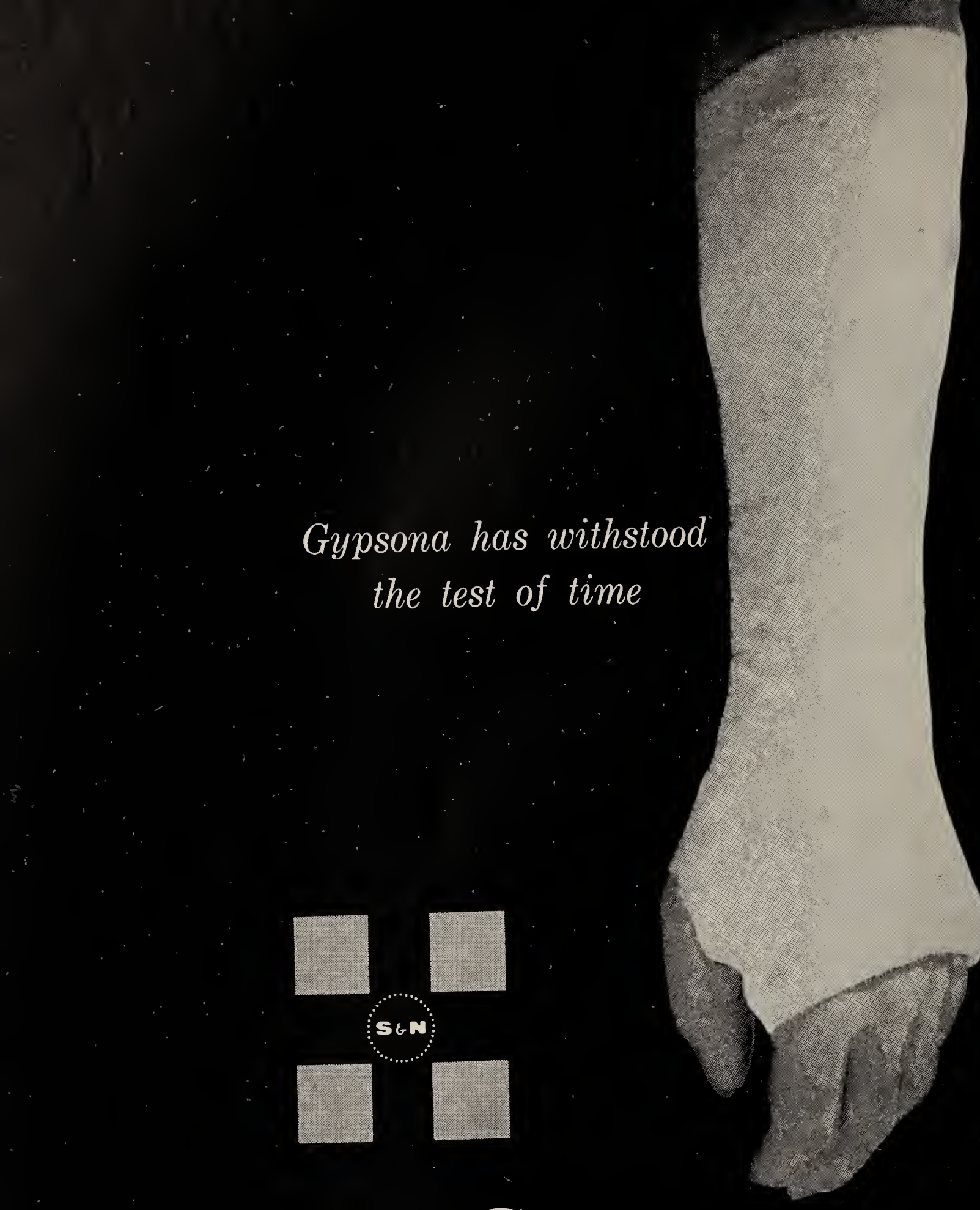

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EDITORIAL

Volume xxxvi, 1958–1959

After five years of devoting issues of the Journal to individual specialties, it has been decided, for this volume at least, to publish issues covering general topics. It is hoped that this change will be a welcome one and that the variety of topics to be presented will prove interesting.

Recently much has been said about the need for more General Practitioners—more family doctors—who know the patient not as distinct functioning systems but as a person whose body and mind react as a whole to disease, whose illness and whose health are both influenced by many factors—his job, his family and friends, his standard of living, his drives, his recreation and his security. We hope to publish several articles in this volume dealing with different aspects of general practice, and indeed it is partly with the purpose of stimulating a *general* interest in medicine to undergraduates and graduates alike that the format of the Journal has been changed.

To the Freshmen

To newcomers to the Faculty of Medicine, a hearty welcome is extended. Freshmen usually find themselves storing the Journal away for reference in their clinical years, and while it is unfortunate that we are unable to publish articles of more immediate interest to them, the main purpose of this Journal is to deal with subjects of a scientific nature, subjects which are often technical by virtue of the fact that much of the material they present is new and the result of extensive research.

A Farewell to Miss Russell

Medical students will be sorry to hear of Miss Olive Russell's retirement from the medical office, after over 40 years of service. Always charming and helpful, she will probably be remembered best for her amazing ability to remember the names and faces of the students, and for following their careers with interest during their undergraduate and graduate years. Many a freshman has been dumbfounded when, on walking into the medical office, he was greeted by name by a handsome, silver-haired lady whom he had never seen before. And many a doctor, out in practice for as long as twenty-five years, has been delightfully surprised when she remembered his name and his activities as a student. The writer can remember a time when Miss Russell was pouring tea at a function for a number of medical people, many of whom had been away from Toronto for years, and was amazed to see her smile and say "Hello", calling each doctor by name and remembering something personal about him.

We wish Miss Russell a happy and healthy retirement. We will all miss her.

P. C. F. M.

PRECEPTOR AND STUDENT

RALPH F. HULL, 5T9

THREE years of clinical experience at medical school acquaint us with most of the specialities, but offer no training in the field of General Practice. Because of this, the College of General Practice, a young and enthusiastic organization of General Practitioners, has offered to final year medical students, the opportunity to participate in a preceptorship plan. Each G.P. involved agrees to take a student for 2 weeks during the summer vacation, to supply him with room and board in his own home, and to show him all aspects of his medical practice.

Only 13 of us at the University of Toronto took advantage of the offer. Job commitments and financial problems prevented many others, who were interested, from taking part. This article is a record of some of the comments of the students, General Practitioners, hospital and University Doctors, patients, and other Medical Journals, about such a preceptorship plan.

We all enjoyed the experience of participating in a general practice. And all of us were surprised at the tremendous variety of problems which confront a family doctor daily. The challenge of making an accurate diagnosis in patients presenting with very early, or atypical, signs and symptoms of disease, was stimulating. In hospital, a diagnosis is usually definitive; in general practice it must often be presumptive.

The long hours of work discouraged some of us. We wondered if it were worthwhile to practice medicine 12 to 16 hours a day, leaving almost no time to enjoy the companionship of one's family, to read, or to be sociable. Only 1 or 2 of us felt we would like a solo practice; several thought that a partnership or group practice would be fine; while the rest believed a specialty would allow more time for leisure.

From a practical point of view, we learned how an office is set up; how the books are kept; how extremely helpful a good nurse is to a busy G.P.; and something of the opportunities for a G.P. to be active in hospital work as part of the volunteer staff, attending out-patients clinics. Such work is non-remunerative, but valuable because of personal contact with various specialists and the stimulus it gives to keep abreast of new developments in medicine.

We all agreed that our preceptorship experience underlined our own inadequacies, particularly in the realm of dealing satisfactorily with emotional problems; on the other hand we felt that the General Practitioner has potentially more opportunity for success in treating these patients because he sees more of the life situation than does a specialist or intern in a hospital.

Very few of the patients exhibited any reticence in discussing their problems before a second "young doctor", or allowing us to be present during the physical examination. All of us emphatically noted that a sympathetic ear, an honest explanation and sincere reassurance, are powerful therapeutic weapons. Many patients expressed the same feelings; that is, they did not like doctors who refused to tell them anything, or who always seemed too busy to hear their complaints.

Our doctor-teachers, and their families who allowed us to intrude on them, felt that the preceptorship plan was filling a large gap in our formal medical education. They wanted us to see how General Practitioners live, medically, socially, and financially, and to reveal some of the satisfactions, as well as the drawbacks, of general practice.

University authorities have mixed feelings about General Practice preceptor-

ships. What the student enjoys doing is not always what is best for him, some say. Others fear that what the medical school strives to instill in students for 3 years—the sciences and laws that are the solid foundation of good medical practice—may be swept away in 2 weeks of association with a sloppy General Practitioner. This is one reason why a preceptorship plan has never been incorporated into the medical curriculum here.

Preceptorship plans are widespread, and their organization varies in different parts of the world. In Manchester, England, a health centre, Derbyshire House, has been set up, with 4 local general practitioners providing medical service to their own patients. Essential ancillary services are available in the same building. Students are assigned to the centre in groups of 4, for 2 weeks. They treat patients at the centre, and at home, and are under the guidance of a G.P.

At the Royal Free Hospital in London, final year students may volunteer to work with a general practitioner 1 night a week, for 3 months, working in his office, and making house calls. They feel there is some advantage in the prolonged length of duty because they can follow the course of diseases better, and come to know some patients very thoroughly.

A third plan is the Home Care programme of Boston University. Final year students are assigned an area near the hospital in which to practise. Patients there are similar to the group eligible for appointments are made through the hospital, and the student visits his patients 6 days a week for 4 weeks. A staff man is available at all times for consultation. Students may prescribe anything but narcotics. The advantages of this scheme are that the student has to stand on his own feet, make his own diagnosis and prescribe treatment, since he is the first doctor to see the patient. He is able, as well, to follow the progress of his patients over a 4-week interval.

As one of our doctors said, it is unfortunate that there are more patients than doctors in Canada, with the resultant temptation for a doctor to be lazy and incompetent, because he has little fear of losing his patients. However, perhaps the most noteworthy observation made by all of us was the high quality of our preceptors. Mostly this was due to the calibre of the men themselves: young, smart, conscientious. But a small part is due to the College of General Practice, only 4 years old, which has an active program of post-graduate education for General Practitioners, and which sets a high standard of continuous study before permitting a G.P. to become, and remain, a member. This is an organization of General Practitioners for self-improvement, which helps not only themselves, but their patients as well.

As students, we had numerous and often conflicting opinions on many aspects of the Preceptorship plan here in Toronto. The program has certainly not convinced all of us that general practice is the best of all areas in which to practise medicine. Others, of course, are more convinced than ever that it is the only field that will give satisfaction.

Two things we all agree on: patients seen in a general practice present problems often never seen in hospital, and provide a real challenge in diagnosis and treatment. We heartily recommend the Preceptorship plan to the younger men in our medical school, and urge them to participate in it when they reach their final year.

ALDOSTERONE

R. H. CURRY, 5T9

What is Aldosterone?

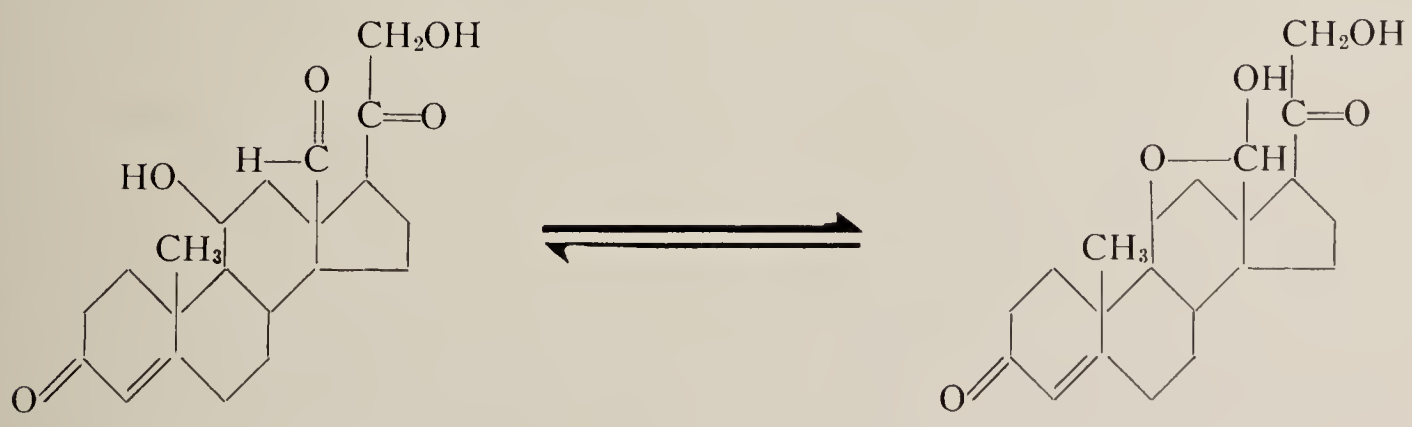
FOR several years an adrenal "amorphous fraction" has been recognized in urine and noted to have a high life-maintaining ability in adrenalectomized rats. DOCA, which for many years was the only adrenal steroid made available in quantity via synthesis was effective in substitution therapy of Addison's disease but it was soon evident that it was only the prototype of a more potent, naturally occuring substance. The "amorphous fraction" did not inhibit growth or produce adrenal atrophy as did corticosterone and its effect on carbohydrate metabolism was weak. Its range of activity was greater than DOCA. Then in 1952 Simpson and Tait re-investigated this fraction and by controlled corticoid replacement therapy in adrenalectomized rats they followed the excretion of labelled sodium and potassium injected into animals. They found the ratio of sodium to potassium excretion was dependent upon the log dose of DOCA and had thereby developed a very sensitive bio-assay method to judge the effect of corticoids on mineral metabolism. They also isolated the substance via paper chromatography.

The stage was set and in 1953 crystalline aldosterone was isolated. Several months later Simpson and Tait published evidence that it was the 18-aldehyde form of corticosterone. In solution it exists in the hemiacetal form and upon oxidation the cyclohemiacetal portion yields a lactone, the German word for which is "Aldos"—hence the term "aldosterone".

Recent studies cite blood levels of aldosterone in the order of .03 microgram/100 ml. Values for urinary excretion of biologically active aldosterone in the normal human are variously estimated from 1 to 7 micrograms/24 hrs, depending largely on the technique of extraction.

Site of Production of Aldosterone

Giroud enucleated rat adrenals from their capsules and incubated the glands and capsules separately in Krebs-Ringer solution with glucose. He noted that the capsules released much greater quantities of aldosterone than the gland and on inspection found that the capsular portion also contained all of the glomerulosa layer and one fifth of the fasciculata layer. He therefore concluded that the glomerulosa layer was responsible



ALDOSTERONE

HEMIACETAL FORM WHICH DOMINATES IN SOL'N

for at least the major portion of adrenal aldosterone. His original findings have recently been confirmed in rat and beef adrenals. Conn, in a case reported in 1956, noted a unilateral adrenal adenoma and a wedge biopsy of the contra-lateral adrenal gland showed atrophy of the fasciculata. There have been other instances of fasciculata involvement in humans with the suggestion that perhaps this indicates a species difference. The situation remains equivocal until results from incubation of human adrenals are available. Lastly, due to an increase in the 24-hour urinary excretion of aldosterone in pregnancy and toxemia, the placenta has been suggested as a possible source of aldosterone. However, at present, the relatively small amount of aldosterone isolated from the placenta as compared with the elevated urinary levels in pregnancy and toxemia suggests that the placenta is of questionable significance in aldosterone production.

Primary Hyperaldosteronism (*Conn's Syndrome*):

Symptoms as originally described by Conn include intermittent muscular pain and cramps (a sign of severe electrolyte imbalance) and gross weakness and paralysis (a sign of marked reduction in intracellular potassium ions). He also noted polydipsia and polyuria with nocturia but no edema. Since then cases have been reported with frank tetany (Conn observed a positive Chovstek's and Trousseau's sign in his original case), and two cases with a severe potassium-losing diarrhea. Subsequently, patients with severe idiopathic edema associated with sodium retention and high urinary aldosterone have been observed but it has not been conclusively established whether this is related to primary hyperaldosteronism or not. Hypertension was noted by Conn and appears to be a relatively constant feature in later cases. Muscle biopsies have shown an elevated intracellular sodium and hydrogen ion content with a decrease in potassium. In the few cases reported to date there appears to be an increased incidence in Negroes.

Blood studies reveal a hypokalemia, hypernatremia and alkalosis. Glomerular and tubular function are reasonably normal with a mild intermittent proteinuria, alkaline urine of low fixed specific gravity and an increased urinary aldosterone level. Renal factors in aldosteronism will be discussed more fully later on.

In Conn's original case, the fundamental pathological lesion was an adenoma of the adrenal cortex. In the cases reported since then many have isolated adrenal cortical adenomas, but at least one case reported an adrenal cortical adenocarcinoma and others have noted adrenal hyperplasia. One unique case reported in Denmark revealed no adrenal abnormality at all.

Secondary Hyperaldosteronism:

This occurs in conditions where there is an increased excretion of aldosterone associated with: (a) generalized edema or fluid collection in one or more of the body cavities, e.g. cirrhosis of the liver with ascites, congestive heart failure, nephrotic syndrome, eclampsia, idiopathic edema, (b) sodium deficient states without edema: e.g.—dietary sodium restriction, intense sweating, salt-losing nephritis, (c) adaption states following surgical trauma, "stress" situations, and familial periodic paralysis in which Conn noted increased aldosterone excretions preceding paralytic episodes.

HYPOALDOSTERONISM:

A pure primary form has been described in the literature. Hypoaldosteronism clearly occurs in Addison's disease and with bilateral total adrenalectomy. Although other secondary states have been noted their full explanation awaits further elucidation of the actual control of aldosterone production and its mechanisms of action.

PHYSIOLOGICAL EFFECTS OF ALDOSTERONE

A. ON ELECTROLYTES:

Fundamentally it is a mineralocorticoid and in normal people produces alterations in the sodium-potassium ion balance. Early estimates indicated that it was 120 times as potent as DOCA in this respect. However, more recent figures indicate that it is 20 to 30 times as effective as DOCA in promoting sodium retention and 5 times as effective in producing potassium excretion. These latter values appear more realistic in view of results from replacement therapy in Addisonians. Due to the sodium retention induced by aldosterone there is a decrease in sodium content of body excretions (urine, saliva, sweat, etc.), and an increase in the total potassium excretion producing an overall decrease in the sodium-potassium ratio of these excretions. Since a decrease in urinary sodium with aldosterone administration has been shown to occur in the presence of an independently increased glomerular filtration rate and therefore increased filtered sodium load, this would seem to indicate an increased tubular absorption of sodium.

B. ON WATER EXCRETION:

Experiments have shown rather convincingly that aldosterone has virtually no effect on water excretion in doses within physiological limits. Adrenalectomized animals or Addisonians failed to excrete a water load and under these circumstances, doses of aldosterone as high as 1 mg. did not restore a water diuresis in adrenalectomized dogs. The therapeutic doses of aldosterone in humans ranges from 150 to 200 micrograms per day. On the other hand, cortisone or whole adrenal extract readily restored a water diuresis.

C. ON CARBOHYDRATE METABOLISM:

Aldosterone will cause an increase in liver glycogen in adrenalectomized rats and has been noted to restore hypoglycemia in Addison's disease to normal blood levels. However, in normal people it appears to have no effect on carbohydrate metabolism with tolerance for I.V. glucose remaining unaltered.

D. ON PROTEIN METABOLISM:

Beck *et al* infused via an intravenous drip, an adrenalectomized female with 0.4 micrograms of aldosterone per minute to a total of 600 micrograms and found that urinary nitrogen increased during the infusion producing a negative balance which rapidly returned to normal following the infusion. Others have noted that with longer periods of aldosterone administration there seems to be no change in nitrogen equilibrium and it is generally concluded that protein metabolism is essentially unaffected directly by aldosterone.

E. ON ACTH RELEASE:

Aldosterone appears to suppress an expected stress-invoked release of ACTH. However, large doses of aldosterone apparently do not effect ACTH secretion in other experimental states and in several normals as judged by ketosteroid and corticoid excretion.

F. ON BLOOD PRESSURE:

Considerable interest has been paid to the possibility of aldosterone acting as an etiological agent in hypertension and much original work on this aspect has been done in Toronto. DOCA, its "physiological brother", will definitely produce hypertension when administered in therapeutic doses in the presence of adequate amounts of sodium. This, coupled with the frequency of hypertension in primary hyperaldosteronism, commonly relieved by removing the adrenal tumor, has provoked much experimental work on this subject. In Beck's experiment outlined above there was no blood pressure change during the infusion of aldosterone. Gornall studied the effect of prolonged aldosterone administration on rats and found that with relatively large doses, the blood pressure was significantly increased above control values in three months and that by five months it reached a plateau level of 75 mm. higher than control values. Controls with DOCA using 50 times the aldosterone dose produced blood pressure levels at five months which were about one half aldosterone-induced levels and the final values were not as high as with aldosterone. The blood pressure levels were not significantly altered by feeding saline solution to the rats. Following up reports that patients with hypertension often demonstrated raised levels of urinary aldosterone, Genest confirmed this fact by subsequent experimentation. It was suggested that this could possibly explain, among other things the hypertension in Cushing's syndrome, the hypertension of primary aldosteronism, the increased sodium in muscles and the aorta of patients with essential hypertension, the correlation between the elevation of blood pressure in hypertensives and their salt intake and finally the beneficial effect in a certain number of hypertensives of a low salt or rice diet. Possibly related to the latter point is an interesting case of primary hyperaldosteronism in a young man reported from Brooklyn who had hypertension antedating his other clinical signs and symptoms by 20 years. A strict salt restriction was instituted for years prior to his diagnosis and may have decreased his positive sodium balance and prevented too great a negative potassium balance, thereby mitigating damage to the kidneys, muscle cells and blood vessels and moderating their functional impairment. His hypertension was relieved by removal of the offending adrenal adenoma. The possibility that prolonged sodium restriction may have caused the tumour must not be overlooked.

Gornall on the other hand has reported that post-mortem heart weights in aldosterone-treated hypertensive rats were 30–40% above control rates after 8 months, indicating hypertrophy. He also noted that in this group of rats, 20% showed proteinuria and, accompanying this, significant renal changes consisting mainly of proliferation of the epithelial cells of Bowman's capsule with some basement membrane thickening, all of which are compatible with the pathological changes in essential hypertension in humans. However, this whole question regarding elevated aldosterone levels in hypertensives is under re-evaluation by the McGill group and it seems probable that, excluding patients on sodium restriction or showing evidence of congestive failure, the remainder of the "essential" group have normal aldosterone excretion. The role of aldosterone in the etiology of hypertension in humans is by no means clear as yet but further developments will prove interesting.

G. ON CONNECTIVE TISSUE:

Selye has shown that aldosterone has a definite anticortosol action by inhibiting the local effect of cortisone in decreasing inflammatory response. However, it does not diminish the involution of the thymus and spleen produced by cortisone. It therefore appears to have rather specific anticortosol action.

H. ON EOSINOPHILS:

A great deal of observations has been made regarding the effect of increasing aldosterone on the eosinophil count. Generally speaking there is no specific pattern of reaction except to heroic doses and the count appears to fluctuate in a fashion not incompatible with the normal range.

I. ON RENAL MECHANISMS:

In adrenal insufficiency, glomerular filtration rate and renal plasma flow are decreased and are restored to normal by cortisone. The sodium-retaining activity of aldosterone is observed with doses which do not repair the depressed filtration rate while much larger doses have been shown to elevate these depressed values to subnormal levels. It has been demonstrated that aldosterone infusion in physiological doses does not significantly alter the renal blood flow or glomerular filtration rate in normal humans. In aldosteronism the glomerular filtration rate is usually normal but some of the tubular functions are altered.

Thus in general, the glucocorticoid effects of aldosterone occur with aldosterone levels which probably are never retained even in severe pathological states.

Polydypsia and polyuria, from experimental studies, appear to be related to the increased loss of potassium and are associated with the "potassium depletion nephropathy" in aldosteronism resulting in an inability to concentrate urine.

The mechanism whereby tetany occurs in alkalotic states such as aldosteronism is inadequately understood. It may be related to the fact that in alkalosis, there appears to be a decrease in calcium ion concentration although the total calcium values are within normal range. It may also be due to alterations in the total ionic balance believed to govern muscle irritability.

Other effects of aldosterone include decreasing the pigmentation seen in Addison's disease and prolonging normal lactation.

CONTROL OF ALDOSTERONE EXCRETION:

A. ACTH:

Since aldosterone is clearly an adrenal corticoid it is of primary interest to discover the relationship, if any, between it and the adrenocorticotrophic hormone. Aldosterone is not under complete control of ACTH. Early workers failed to show significant increase in aldosterone levels with ACTH administration. However, Beck & associates later published evidence that there was a definite rise in aldosterone level in normal individuals related to ACTH infusion and this was maintained 24 hours following the infusion. Others have confirmed this but it is not an invariable finding. The discrepancy is attributed in part at least to improved methods of assay. There is also evidence that prolonged ACTH therapy decreases aldosterone production in rheumatoid arthritis and in nephrotic syndrome. Conn demonstrated the effect of ACTH on the excretion of sodium in his original case and following initial retention there was a natruresis while ACTH was still being administered. He related this to the type of picture seen in treatment of nephrotic syndrome and concludes by

saying: "It would appear that in the presence of excessive activity of aldosterone, elevation of the 17-hydroxy-corticoid levels acts as an antagonist to aldosterone with respect to the direction in which sodium ion moves across cell membranes". Giroud later indicates that the action of ACTH on aldosterone secretion appears to be conditioned by changes in extra-cellular volume. Patients with panhypopituitarism have been shown to excrete normal amounts of aldosterone in the face of decreased amounts of other corticoids. These patients frequently do not show an increase in aldosterone following ACTH presumably due to adrenal cortical atrophy.

B. SODIUM:

Salt depletion in normal subjects, accomplished by various methods, is accompained by a definite increase in aldosterone levels. The reverse is true of sodium loading.

C. POTASSIUM:

Laragh and Stoerk have shown that an excess of potassium in dogs produces a marked increase in aldosterone. Others failed to demonstrate as dramatic effects in humans. Potassium administration produces sodium loss but these changes take place within the cell primarily and this may help explain the absence of edema in Conn's syndrome despite considerable sodium retention. Conn found that attempts to replete his patients with potassium immediately resulted in potassium retention and sodium excretion. After four days however resistence was met and in spite of large doses of potassium by mouth, increased potassium excretion returned with sodium retention. Others have observed this also. Possibly the potassium resistence is due to an inability of cells to release an excess amount of intracellular sodium which is being held there by increasing aldosterone levels further aggravated by potassium administration.

D. SODIUM-POTASSIUM INTAKE RATIO:

At first this was believed to be of significance in controlling aldosterone secretion. At present its significance is doubted.

E. TOTAL FLUID VOLUME:

Changes in body fluid appear to be crucial in many instances. Administration of pitressin to normal individuals with adequate fluid intake produced an increase in body water and hemodilution, with raised 24-hourly urinary sodium and decreased aldosterone. On cessation of pitressin administration, serum sodium returned to normal and was accompanied by a decrease in urine sodium and an increase in urinary aldosterone. This does not appear to be a direct effect of pitressin. If the increased aldosterone is a response to sodium depletion, why is there no increase in aldosterone excretion during pitressin administration particularly at the peak of the negative sodium balance when the increased water retention produces a decreased sodium concentration in the face of increasing total sodium excretion? Since potassium levels stayed within normal range throughout, the sodium-potassium ratio would tend to fall and produce an increased aldosterone secretion during the water retention period, if it were a critical factor. Thus the aldosterone level appears to be secondary to alterations in hydration, an increase in fluid tending to depress aldosterone production and vice-versa. Why

then, in edematous states, is there a secondary increase in aldosterone? Possibly it is because there is a decreased intravascular volume even though the extra-cellular fluid volume is expanded. A lowered intravascular volume is known to be present in nephrosis, cirrhosis, etc.

F. INTRAVASCULAR VOLUME:

A normal healthy individual was maintained and regulated on a low salt diet for 3 days. On the third day intravenous infusion of 200 ml. of albumin produced a sudden expansion of blood volume and the subsequent decrease in aldosterone excretion was noted in spite of a low salt diet. It appears in this instance at least that intravascular volume changes overruled the expected effect of sodium depletion. Recently reported studies appear to confirm the fact that in normal individuals, aldosterone excretion decreases with expansion and increases with contraction of intravascular volume. In the above experiment, the glomerular filtration, if affected, should rise with intravascular expansion and fall with contraction, thereby tending to antagonize the observed results. Therefore, the changes seen probably reflect alterations in the blood volume and are not due to changes in renal hemodynamics and function. Bartter and his associates in 1956 showed that in normal patients the use of mercurial diuretics, due to their rapid action, did not appreciably alter intracellular tone or fluid content in the early stages following administration and that there were insignificant changes in serum sodium. In effect, the extracellular and presumably intravascular volume was all that was primarily affected by these drugs and early in the diuresis, there was an increased aldosterone production. Unfortunately, this inverse relationship between aldosterone levels and intravascular volume is not always so obvious. But does this help to explain secondary hyperaldosteronism? Perhaps some portion of the intravascular volume may act as an "effective fluid volume" and provide the afferent stimulus for the eventual release of aldosterone.

G. "EFFECTIVE FLUID VOLUME"

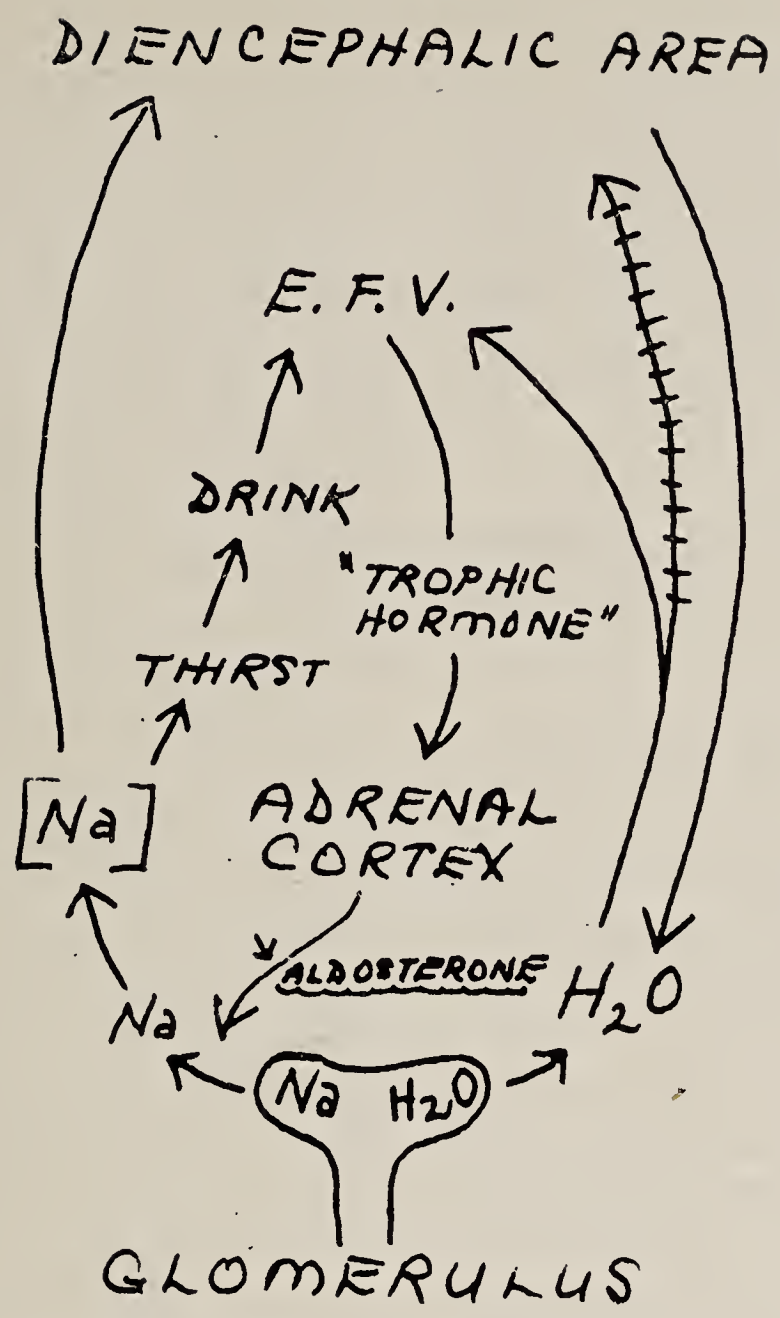
There is evidence that liver disease predisposes to elevated aldosterone levels but it does not solely account for the marked increase in patients with ascites. This has been observed as early as 1953. The highest levels were seen in the acute development of ascites following abdominal paracentesis. Many factors may play a part in this including shift of sodium and water, plasma volume, renal function and extra- and intra-cellular tonicity. Transudation of sodium and fluid into the abdominal cavity produces a decreased blood volume. Thus, there appears to be a transitory shift of intracellular sodium into the extracellular compartment as demonstrated by a relative loss of sodium from erythrocytes following a decrease in plasma osmolarity at this time. These changes are probably all secondary to the initial decrease in blood volume. There is also an observed increase in urinary aldosterone and renal sodium retention. This subsequently produces an increase in total body sodium and extracellular tone which is eventually transmitted to the cells producing an increase in the sodium and water content of the cells following the initial decrease. Fluid, if given intravenously during the stage of accumulation of ascites, produces a demonstrable decrease in aldosterone secretion during the period of intravascular expansion. Thus it may be that aldosterone controls body sodium and

the resulting fluid volume changes affect the secretion of antidiuretic hormone. During ascites formation, retention of sodium and water fails to depress aldosterone secretion and this may conceivably be due to the loss of sodium and water into the peritoneal cavity which is insensitive to sodium and water changes. In this respect the ascitic fluid appears to be an "ineffective fluid volume" but in the sense that it concurrently depletes the plasma volume it is an "effective fluid volume".

Much work has been done on the mechanism of production of hyperaldosteronism in heart failure, space permitting only brief mention of the salient points. Lately results from cardiac catheterization show generally increased urinary aldosterone with high central venous pressure. An increase in venous pressure leads to a decrease in intravascular sodium and water with edema formation. This may in part produce the increased aldosterone secretion for it has been observed that with adequate digitalization and salt restriction, the edema is relieved, sodium and water return to the intravascular space and aldosterone levels drop to normal. In addition, relief of venous pressure by venesection was followed by a transitory increase in efficiency in the myocardium and a restoration, temporarily, of normal blood, fluid, electrolyte and aldosterone values. Cardiac catheterization has also shown that most patients with decreased output show urinary hyperaldosterone excretion. This lends support to the possibility that the "effective fluid volume" is the arterial volume and that changes in certain parts in the arterial tree may stimulate a volume receptor the anatomical site of which is still debatable. This may be the stimulus for release of a specific trophic hormone which subsequently provides the afferent stimulus for aldosterone secretion. Probably changes in the deposition of both sodium and water throughout the body, associated with changes in arterial volume and flow, are involved in this mechanism of aldosterone secretion.

H. TROPHIC HORMONE:

As yet the afferent pathway for the transmission of impulses from a volume receptor has not been established. However, Rauschkolb demonstrated evidence that possibly there was a trophic hormone elaborated from the diencephalon. Farrell showed that hypophysectomized dogs secrete aldosterone at 66% of normal levels while decerebrate dogs showed a reduction of 25% of normal. Aldosterone levels were not affected by decortication. Subsequently a neurohumeral aldosterone-regulatory center located in the supra-optic hypophyseal area was postulated. Lately, it has been shown that extracts of beef diencephalon infused into decerebrate dogs restored aldosterone secretion to normal. As a result of these studies it was thought worthwhile to investigate the activity of various extracts from this area on incubated adrenal glands. Giroud found that a single batch of Infundin, an impure hypothalamic-posterior pituitary extract, stimulated a significantly increased aldosterone production in vitro. Pure extracts of the known constituents of this extract did not appear to have sufficient activity to account for the total increase and it is therefore possible that there is some controlling hormone in this preparation. Experiments with the remainder of this batch are presently being conducted on humans to observe their effect on aldosterone excretion. From the above data we can for the time being sum up diagrammatically:



Other Controlling Factors Include:

I. stress:

College students preparing for examinations have been shown to excrete increased amounts of aldosterone in relation to the amount of subjective stress experienced.

J. growth hormone:

This appears to stimulate aldosterone excretion also. Growth hormone when administered to panhypopituitary dwarfs has been shown to cause an increased aldosterone production.

K. pregnancy and toxemia

Aldosterone levels rise in pregnancy and quickly return to normal levels postpartum. Changes in water and electrolyte distribution cannot be ignored as a possible explanation (e.g. sodium requirements of the fetus). It has also been observed that other corticoids rise proportionately during a pregnancy and will in certain states promote sodium excretion. Thus aldosterone appears to be "tuned in a higher key" to maintain water and electrolyte balance. Originally aldosterone levels in toxemia were thought to

be considerably higher than in normal pregnancy. In fact, they appear to be equal, and in some cases, lower. However, in toxemia other corticoids appear to be significantly reduced and the relative excess of aldosterone may lead to water and sodium retention with edema.

L. MID BRAIN:

This may in future be more definitively demonstrated to have some control over aldosterone secretion.

RENAL STATUS IN HYPERALDOSTERONISM:

Pathology reports in patients with Conn's syndrome in addition to varying degrees of hypertensive nephrosclerosis have noted that the epithelium of the proximal tubules was transparent, distorted, heaped-up and vacuolated. These changes were seen in a much less marked degree in the distal tubules and collecting tubules. The nephron changes are remarkably similar to those noted in other potassium deficient states and resemble the characteristic "vacuolar nephropathy". These changes appear reversible up to a point as has been shown from post-operative results on urinary excretion and blood pressure changes. Observations on experimental animals in which potassium deficient states have been induced demonstrate a similar kidney lesion to that seen in humans except that the most severe damage appears to be located in the collecting tubules and distal convoluted tubules. This has led some to believe that there may be a functionally important lesion in the human collecting and distal tubules which is not as yet histologically apparent.

A. EXCRETION OF SODIUM AND POTASSIUM:

At present it is thought that virtually all potassium is absorbed from the tubular filtrate in the proximal tubule, and actively excreted in the distal tubules. Even in cases where tubular function has been significantly impaired by potassium depletion nephropathy, renal conservation of potassium may still be very efficient. Potassium is actively excreted in the distal tubule and for this mechanism to function effectively there must be sodium available in the distal tubular filtrate. Therefore in any condition where there is a decreased renal blood flow as in heart failure with decreased cardiac output leading to a decreased glomerular filtrate, it is probable, providing kidney function has not been too severely embarrassed, that there will be maximal absorption of sodium proximally (normally 80–85%) and less sodium available for potassium exchange distally. Thus, the potassium depletion would be less severe and in fact, this appears to be true. From this it seems reasonable that a low sodium diet with increased aldosterone secretion would deliver a decreased sodium load to the tubule producing a relative increase in sodium resorption proximally and a decreased cation exchange distally thereby conserving potassium. It is interesting to note that in the lesion associated with primary hyperaldosteronism, the excretion of sodium loads is rapid and edema does not usually occur. This may be due to the higher filtration rate seen in this type of potassium deficient nephropathy as opposed to other types.

B. REGULATION OF ACID-BASE BALANCE:

Normally the secretion of potassium in distal tubules is governed in part by the hydrogen-potassium ion ratio in the tubular cell and in a potassium deficient state there is a decreased output of organic acids with a relative increase in hydro-

gen ion output and ammonia formation resulting in the so-called "paradoxical aciduria of alkalosis". Why then, in primary hyperaldosteronism, do we see an alkaline urine resistent to acidification? In the alkalosis of potassium deficiency the urine contains less bicarbonate than would normally be expected at similar plasma bicarbonate levels under other circumstances and in this sense, there is a "paradoxical aciduria". It may also be due to the fact that ammonia excretion appears to be increased and the urine becomes alkaline despite continued excessive hydrogen ion excretion. It is known in addition that potassium occurs in the unionized form in cells and it is postulated that even in a potassium deficiency state, aldosterone may have a specific effect on the renal tubules in stimulating an increased liberation of organically-bound potassium as potassium ion and therefore maintaining an increased potassium level in these cells, in the face of total body potassium depletion. The primary effect of aldosterone on increasing tubular resorption of sodium proximally also cannot be ignored. Nicholson feels that in low doses, aldosterone may have its major effect upon the proximal mechanism and little effect directly on potassium excretion. In any event we are faced with a type of "renal tubular acidosis" (accumulation of hydrogen ions in tubule cells) which is an entirely non-specific tubular disorder occuring in a variety of renal diseases. Another interesting observation is that patients with chronic renal disease may develop a salt losing nephritis, (due to tubular damage), one cause of which can be prolonged potassium loss. In such states experiments indicate that these people when repleted with sodium supplement remain in salt balance but excrete massive amounts of aldosterone. This would indicate that the continued stimulation by sodium deficiency may lead to increased aldosterone secretion which outlasts its original stimulus. The adrenals of patients dying with "salt-losing nephritis" often show gross enlargement and in some instances nodular hyperplasia has been noted in the cortex.

Thus the overall effect of potassium depletion seems to produce a paradoxical effect on the renal tubule. On the one hand, there is an increased threshold for bicarbonate excretion and a tendency to an increased ammonia production and excretion both of which suggest an acceleration of hydrogen ion excretion resulting from the alteration in intracellular potassium-hydrogen ion ratio. On the other hand, there is a tendency for urinary pH to be alkaline with a consequent loss of modest amounts of bicarbonate in the urine indicating a defect in hydrogen ion excretion. The exact explanation for this is not at all clear. Among other things, it may be that these represent two independent but complementary changes in kidney tubule function, one in the proximal tubule and the other distally. Suffice it to say that the actual mechanism of aldosterone action on the kidneys is at present inadequately understood although theories abound. The significance of aldosterone in disease is even more vague. In any case, aldosterone appears to be the "fine adjustment" or "permissive factor" superimposed on a powerful mechanism which is completely obscure at present but which probably accounts for about 85% of normal sodium resorption, is responsible for the diurnal rhythm of sodium excretion and initiates acute renal adjustments in sodium excretion which appears to be entirely independent of aldosterone.

Metabolism and Excretion:

There is strong evidence that aldosterone is metabolized to some degree at least in the liver. No other organ has yet been incriminated. It is excreted in the free and conjugated forms and probably other breakdown products which have not yet been isolated but may soon be identified. It can be extracted from the urine by acid-hydrolysis with beta glucuronidase and assayed. It also has a characteristic chromatographic pattern demonstrated by various techniques.

Comment:

An attempt has been made to summarize some of the material reported in the literature on this topic. Rapid changes and advances in concepts are to be expected. It must also be remembered that many of the theories outlined here *are* just theories, and have yet to be conclusively proven or disproven.

Acknowledgement

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CLINICAL APPLICATIONS OF FREE TISSUE TRANSPLANTS

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A. Purpose

THE purpose of this article is to outline some of the clinical applications of tissue transplantation. This is a topic which links fundamental histology with some of the most recent advances in surgery. Consequently it is not presented in a unified and simplified manner to us as students. It is a vast and rapidly changing field and therefore the author will try to present the more fundamental concepts while merely pointing the way to the newest developments.

B. Some Definitions and Their Significance

The first fundamental distinction to have clearly in mind is that between free grafts and pedicle grafts. A pedicle graft is not severed from its blood supply, while a free graft is completely separated from its blood supply. Except for a few instances, pedicle grafts will be excluded from this discussion, because this term not only applies to skin, (e.g., cross-leg pedicle grafts), but has analogies in all surgery involving the shift of tissue. For example—the shift of muscles in the hand to replace a lost function (usually opposition), the shift of the hypoglossal nerve to attempt to overcome a facial palsy, or even the shift of bowel to stomach in a partial gastrectomy—all of these may be regarded as pedicle grafts. Therefore this discussion will be limited to free grafts.

Free grafts may be classified as autografts, homografts, and heterografts. Heterografts are from one species of animal to another and have only experimental applications at present.

Autografts (auto=self) are from one part of the body to another part of the same body. They make up the majority of free grafts used clinically because the surgeon can rely on these grafts surviving since they contain no antigens foreign to the host to incite an allergic response.

Homografts (homos=same) are transplants from one member of a species (in which random breeding has been practised) to another animal of the same species. Random breeding is important because tissues may be transplanted successfully from one animal to another if the strain has been inbred very closely so that their tissue antigens are "identical". This has its counterpart in the identical twins of the human species. Although these are cited as examples of homografts which survive they are in reality virtually autografts since their tissues contain the same antigens. The fate of homografts differs from that of the autograft—they are either replaced or rejected by the host. They do not survive intact. If the function of the graft is purely mechanical, such as fascia, tendon, bone, cartilage, cornea, arteries—then this replacement does not matter for the graft has fulfilled its purpose as a temporary support. Moreover these transplants often serve to stimulate their own replacement by host tissues (e.g., "induction" by bone chips). These grafts are called "homostatic" by Longmire because the cells do not have to survive for the graft to fulfill its function. It will be noted that these tissues are composed mainly of intercellular substance, a non-living material which is not rejected by an immune reaction, so that the graft is slowly replaced by the host.

However if the homograft cells must survive in order for the transplant to fulfill its function, then this is a vastly different problem. Such tissues are skin, endocrine glands and kidney which are called "homovital" grafts by Longmire.

These grafts do not succeed because the cells are destroyed by an immune reaction to the foreign proteins which the graft contains. However homograft skin (and kidneys) have been used occasionally as will be mentioned later.

Much work is being done in the field of so-called "depressed immunity", to see if these "homovital" homografts can be made to survive. The decreased antigenic potential of foetal tissues is being explored in the field of endocrine transplants, as well as the decreased immune response in embryos and in children with congenital agammaglobulinemia.

Certain agents such as hydrocortisone and ACTH are being used to attempt to suppress the immune reaction (e.g., in corneal transplants, severe burns). Total body irradiation to destroy the bone marrow and depress the immune response has been done experimentally and even tried clinically to allow the homotransplantation of bone marrow to patients with end-stage leukemia. The Transplantation Bulletin contains articles on all new developments in this field. A final question to be considered is that of fresh versus preserved grafts. Almost all autografts are fresh although this is not necessary for success. In the case of homografts the question is simple for if the cells of the graft must be alive for the graft to function (e.g., skin), then fresh tissue should be used. However if it is not necessary for the cells to be alive, then preserved grafts are just as good (e.g., bone, vessels, fascia). In fact, preserved homografts of vessels are thought to be better than fresh ones because they have less tendency to be rejected after the cells have been destroyed.

From a consideration of these fundamental aspects of tissue transplants, we can see that a surgeon who is selecting a tissue transplant must consider first of all what function the graft must serve. This question gives clinical significance to the term "autograft"—for the surgeon can rely on these tissues surviving and functioning as they did in their original site. Thus the majority of tissue transplants are autografts. The question of function is also fundamental to our understanding of the use of homografts. These tissues are replaced or rejected by the host—but if the function is purely mechanical then this replacement does not matter. Such tissues are bone, fascia, blood vessels, etc. (homostatic). However if the cells of the homograft must survive and function in order for the graft to succeed then this transplantation is a complex and unsolved immunological problem. Such tissues are skin, endocrines, and kidney (homovital).

C. Organization

A basic approach to the problem of tissue transplantation may be gained by considering the four basic tissues of which the body is composed. The tissues to be considered are listed under each broad group:

I. Connective tissue—fascia, tendon, cartilage, bone, cornea, blood vessels.
II. Muscle tissue
III. Nervous tissue
IV. Epithelial tissue—Covering and lining: skin and dermis.
—Glandular: endocrine.

In each case, the type of graft, the transplant, and the fundamental clinical applications will be mentioned.

I. Connective Tissue:

First let us discuss the various types of connective tissue which find a multitude of clinical applications, keeping in mind that the basic functions of connective tissue are those of support and of binding tissues together. Many of its uses can be related to these functions.

In reading about the uses of fascia and tendon the names of Gallie and

LeMesurier (of Toronto) crop up again and again. It was they who referred to these materials as "living sutures" and this concept forms the basis for many of the operative procedures which they devised and developed.

1. *Fascia*: There is a ready supply of fresh autogenous fascia in the fascia lata of the thigh which can be obtained by use of a fascial stripper with only one incision. Its uses are three basically:

(a) As a substitute for ligaments, e.g.,
  (i) habitual dislocation of the patella,
  (ii) recurrent dislocation of the shoulder,
  (iii) dislocation of the sternoclavicular joint,
  (iv) as a sling to prevent bowstringing of tendons,
  (v) as several slings to correct a facial palsy.

(b) As a sheet or membrane, e.g.,
  (i) any defect in anterior abdominal wall (various types of hernia),
  (ii) a defect in the dura mater.

(c) As a suture material, e.g.,
  (i) in repair of inguinal and femoral hernias,
  (ii) in repair of a torn Achilles tendon.

2. This leads into the other type of "living suture" to which Gallie referred, namely *tendon.*

In tendon grafting, the paratenon or loose areolar tissue surrounding the graft is usually included to allow gliding and to permit the early development of circulation, both of which are essential to prevent healing with excess scar tissue and adherence to the surrounding tissues.

Obviously since there is some doubt about the strength and viability of the graft in any case, we must use the best material available which is always fresh autogenous tendon. The usual sources of tendon grafts are the palmaris longus and the long extensors of the toes.

Gallie advocated the use of tenodesis or tendon fixation for deformities resulting from polio, but almost the only use of tendon grafts at the present time is in the replacement of flexor tendons in the fingers. Bunnell gives an excellent account of this procedure in his textbook.

3. The next type of connective tissue is *cartilage* which is one of the most inert substances for grafting. Consequently fresh (or preserved) homografts of cartilage can be used since they are slowly replaced and their function is purely mechanical. Theoretically a fresh autograft is still preferable since at least the surface cells which are nourished survive intact, but obtaining a rib cartilage may convert a minor procedure into a major one.

As mentioned, the common source of cartilage grafts is the costo-chondral cartilage of ribs, although ear, septal and alar cartilages have been used.

The principal use of cartilage grafts is to correct deformities of the nose (such as saddle nose), of the mandible, or of other facial bones.

Lyndon Peer advocates the wider use of diced cartilage grafts by shaving a rib cartilage into small pieces which can then be molded like wet sand. He says that the use of these grafts is based on a simple law, namely that connective tissue cells (fibroblasts) abhor unlined dead spaces like nature abhors a vacuum and consequently invade the spaces between these shavings of cartilage and weld the graft into a solid unit. Diced cartilage grafts may be used to fill out skull depressions instead of a plate, to cover the bony defect in spina bifida with cord herniation, and to reconstruct an ear. This latter is an interesting procedure in which a perforated vitallium

ear mold is filled with diced cartilage and buried in the abdominal wall for five months. By this time a cartilage mold of the ear is formed inside the metal and may be removed and placed under the skin on the side of the head.

4. One of the most widely used connective tissue grafts is of course *bone*. John Hunter first observed in the 18th century that separated fragments of bone could survive and grow. This property of bone is responsible for the many ingenious uses to which surgeons have put this tissue.

The form which bone grafts may take are of three general types: (a) cancellous bone chips, which are most widely used, are obtained from the ilium, and form a bony union in 8–14 days; (b) dense (compact) cortical bone obtained from the tibia or iliac crest which forms a strong union but requires longer immobilization, and (c) a combination of cortical and cancellous bone obtained from the ilium which combines good strength with moderate healing time. As noted, the sources of material are ilium, tibia and rib.

In considering dense cortical bone, fresh autogenous grafts are still the best material because the surface cells may survive intact. However freeze-dried homografts are very widely used because of their availability from the bone bank. These grafts are replaced by "creeping substitution" of new bone and simultaneously the dead bone of the graft is resorbed so that the histological structure eventually becomes identical to the host. Where there is some doubt about the graft succeeding due to other variables such as infection or questionable blood supply, fresh autogenous bone should be used if possible and the unnecessary use of homografts is usually avoided. On the other hand, a tibia from which massive autografts have been taken may be slower to recover its function than the original injury and is subject to secondary fracture, so that both autografts and homografts must be considered.

In general either type of cortical bone graft, to succeed, must be (a) placed in contact with living bone, (b) immobilized until bony union occurs and (c) used functionally after healing.

There are three important uses of bone grafts which will be outlined briefly, (a) fusion of joints, (b) to fill defects in bone and (c) to correct cases of non-union in fractures.

(a) The use of bone grafts in the fusion of joints immediately calls to mind the widespread use of spinal fusion for various conditions. Bone grafts are used in the form of an H-shaped iliac graft or twin tibial grafts combined with cancellous bone to fill the crevices and wiring, (where necessary), to immobilize the grafts while the bony fusion with the vertebral column occurs. Cancellous bone chips alone are also used in the arthrodesis of any other joint in the body.

(b) To fill defects in bone, cancellous bone chips from the ilium are used for example after the saucerization in cases of osteomyelitis, or after curettage of cavities created by benign bone tumours (which may have caused pathological fractures).

(c) However it is in the field of traumatic fractures that bone grafts have found most of their uses and Watson-Jones has an excellent chapter in his text dealing with this aspect of their use. He stresses the point that in all cases of non-union, the fracture will unite eventually, if the bone surfaces are freshened and the fragments immobilized for a long enough period. Immobilization may be achieved by means of a bone graft, but this is no longer accepted as the best means of immobilizing an ununited fracture. It has been replaced by fixation simply with a plaster cast, or with intra-

medullary nails or screws and plates, combined with cancellous bone chips to promote osteogenesis and bony union. MacNab (of Toronto) and others feel that it is better not to disturb the site of non-union by freshening the bone ends unless there is associated malunion. They use onlay grafts of slabs of cancellous bone placed around the site in a barrel-stave fashion to bring about bony union.

Thus the more complicated methods of bone grafting such as the various inlay grafts (diamond sliding) are becoming out of date. However, onlay grafts of cortical bone, usually tibia, with screw fixation are still widely used, especially where the defect is large. But as mentioned, the damage to the tibia which donates the graft, and the chance of secondary infection due to the screws or fracture of the graft must not be forgotten.

Since fresh cancellous bone from the ilium is the most commonly used graft we must thoroughly understand its applications. It stimulates osteogenesis of surrounding cells and promotes early bone formation by its own covering cells which survive transplantation. This action of "induction" is now recognized as the most important function of bone grafts, since immobilization can be achieved better by other means.

Moreover when there is actual or potential infection, cancellous bone only should be used. Because of the slow absorption of compact bone, it acts as a foreign body and will serve as a sequestrum to cause persisent infection.

In summary, cancellous bone chips are used (a) for ununited fractures anywhere to promote new bone formation (in conjunction with another means of immobilization); (b) as a supplement to tibial or iliac onlay grafts in spinal fusion or in large bony defects; (c) alone in the presence of infection where cortical grafts will fail; (d) in arthrodesis of any joint; and (e) to fill any defect in bone.

5. One of the most recent developments in tissue transplantation is that of *transferring bone marrow* from one person to another as was mentioned earlier. So-called homografts between people of identical blood groups are used. They have been utilized in cases of aplastic anemia to tide the patient over until his own marrow regenerates, or in cases of leukemia after total body irradiation, to replace the leukemic tissue destroyed by the X-rays. There is little success as yet in re-populating the patient's marrow.

6. The next type of specialized connective tissue to be mentioned is the *cornea* which is a one millimeter thick membrane composed of a clear stroma of collagen and mucoid intercellular substance and covered by a layer of epithelium on one side and endothelium on the other.

Since the author knows little about the intricacies of keratoplasty, only a few facts will be mentioned. The indications for its use are (a) *optical*—to restore vision by replacing an opaque scar; (b) *therapeutic*—to aid in the healing of an indolent corneal ulcer by the application of fresh tissue; (c) *cosmetic*—to replace the white scar of a blind eye.

The criteria of success of the homograft is anatomical transparency. The types of optical grafts are (a) *full thickness*, which is dangerous since it opens the eye and is only about 30% successful; (b) *lamellar or split thickness*, which is not dangerous and is about 70% successful; (c) *collar button*, which is a combination of the other two and is quite satisfactory.

The factors which influence the results are:

1. Technique—there must be exact fixation.

2. Infection—A culture of donor cornea is taken and any lid infection from the host is removed.

3. Host Cornea—selection of cases. The type of scar influences this, for burn scars are notoriously difficult, while scars from conical corneas of interstitial keratitis are much better.

4. Donor cornea—obtaining and preserving fresh specimens is a big problem.

5. Vascularization and Edema—these indicate rejection of the graft if they persist. An aqueous suspension of cortisone is used to attempt to prevent this.

In considering corneal homografts, it was thought that they survived intact because of the position and nature of this tissue, nourished as it is only by aqueous humour and composed mainly of non-living intercellular substance. But Ham states that these grafts do not survive any more than do cortical bone grafts but are replaced by the host—the epithelium and endothelium rapidly and the connective tissues stroma more slowly.

7. The last type of graft to be considered as specialized connective tissue is that of *blood vessels*. One of the most rapidly expanding fields of surgery is that of vascular surgery and this expansion has to a great extent been due to the use of arterial homografts.

Although in many centres these grafts are being replaced by plastic prostheses, the use of the homograft is still widespread. Arterial grafts are preserved as freeze-dried specimens and it has been found that these non-viable grafts give better results than the viable ones because of a decreased immune reaction by the host with less tendency for rejection of the graft. The criteria of a good result are the ability to transmit an adequate amount of blood for a long period of time without rupture, aneurysm formation, thrombosis, or stricture. These grafts are entirely replaced by the host eventually, although the intercellular substance and especially the elastic laminae last 6–9 months.

As in the case of the cornea, homografts are essential in vascular surgery, the only autogenous grafts available being veins such as the saphenous, which may occasionally be used to substitute for smaller calibre arteries, such as the femoral. Indeed this is the way in which vascular grafting began.

The clinical applications of arterial homografts are many. Their use may be considered whenever a major vessel is malformed, weakened by disease or occluded. This includes such clinical situations as (a) segmental damage to a vessel from trauma, intractable spasm after a fracture, or formation of an arterio-venous fistula; (b) segmental occlusion from thrombosis on atheromatous plaques or embolism, the patency of the circulation proximal and distal to the occlusion being established by arteriography and a bypass inserted, rather than removing the diseased segment; (c) replacing segments of the aorta because of aneurysm formation or blockage by thrombosis.

Other less frequent uses are in (d) coarctation of the aorta; (e) replacement of the renal arteries in hypertension due to unilateral or bilateral narrowing of these vessels; (f) Buerger's disease, if limited to a segment.

II. Muscle

Free muscle grafts are always replaced by fibrous tissue and are only occasionally used to stop bleeding from blood vessels where ligation is not advisable—such as the surface of the brain.

To survive, muscle grafts must have their blood supply and motor nerve supply intact and in this state they are analogous to pedicle grafts of skin. In this form the surgeon makes ample use of muscle grafts for example, (a) in the eye for correction of strabismus or ptosis; (b) in surgery of the hand and orthopedics where muscle with tendon is shifted to substitute for absent or para-

lysed muscle or to move and stabilize a joint; (c) in plastic surgery, to move skin in facial palsy; (d) to correct destruction of the sphincter ani by graft of gracilis; (e) Dr. Mustard's work on polio patients by shifting the psoas major to substitute for the weak gluteus medius.

III. Nervous Tissue

The clinical uses of nervous tissues as a tissue transplant are definitely limited. Thin, short autografts (using a cutaneous nerve) will survive, undergo Wallerian degeneration and form new Schwann tubes to conduct nerve fibres across the gap into which they have been inserted. It must be remembered in nerve grafting, that the graft must not only survive, but must survive in a form that can provide a suitable pathway for new fibres, because the function of a nerve graft is to guide new nerve fibres from the proximal stump into the Schwann tubes of the distal stump.

Nerve homografts are not used clinically because they almost invariably fail. Nerve autografts are not used if it can possibly be avoided by stretching or moving the nerve, but do find some use in peripheral nerve injuries where there is a gap in the continuity of the nerve. As well as the survival of autografts, the source is also a problem and to replace a large nerve it is often necessary to make up a cable graft of strands of the sural nerve, anterior cutaneous nerve of the thigh or even intercostal nerves. These cable grafts are better than a large graft because they permit the blood supply to reach each fibre. One series of nerve autografts reported in 1948 gives the results of 58 cases, 26 having complete recovery, 5 partial, 14 failures and 13 too early to report. Bunnel reports better results in using single strands of the sural nerve to substitute for digital nerves in cases of finger trauma.

IV. Epithelial Tissue

The other tissues left to mention are skin, endocrines, and kidney—all of which are homovital grafts in that the cells of the graft must survive if the graft is to fulfill its function. All of these tissues may be transplanted successfully as autografts.

The kidney will be mentioned only to say that the only successful homograft has been between identical twins and perhaps this is really an autograft. True homografts functioned for an average of 6 days after transplantation in one series although longer survival has been reported in some cases.

Accordingly, to conclude this article, discussion of the fourth great body tissue, namely epithelium, only remains. This may be covering and lining, or glandular, and brings us first of all to the great field of skin grafting.

The technique of skin grafting has been known for centuries but its use has expanded greatly since the development of the split thickness graft. As mentioned earlier, this discussion will be confined to free skin grafts, the use of pedicle grafts being omitted. They are used where full thickness skin is needed or good cosmetic results are essential. Throughout, autografts will be referred to unless otherwise stated.

There are 2 main types of free skin grafts:

(a) *The full thickness graft*, which has the advantages that a suitable colour, hair distribution and thickness may be chosen; it gives a good cosmetic result with little scarring; and it has good weight-bearing qualities. Consequently it is used mainly on the face, hands and other weight bearing areas. It has the disadvantages that the donor site, if large, will require grafting and that one is less sure of it "taking", due to the difficulty in surviving by diffusion of tissue fluid while establishing a circulation with the host tissue.

(b) *The Split thickness or Dermatome graft*, may be cut to any desired thickness. Ham emphasizes that even split thickness grafts contain a good deal of dermis. The thinner grafts are often used in children and over granulating areas where thicker grafts will not take due to infection or decreased blood supply. The thicker grafts (about 16/1000 of an inch) are used for most all-purpose grafting. Split thickness grafts may also be cut into small pieces called "island grafts" or "stamp grafts" about one half inch square. These are used to cover small areas of the first graft which did not take, or if there is a shortage of available skin, e.g. in burns. However they result in more scarring.

Split thickness grafts will survive on fat, muscle, fascia, paratenon, periosteum or cancellous bone since these tissues provide sufficient blood supply, and also on granulating surfaces which are properly prepared by removing any exuberant or necrotic tissue. However bare tendon or cortical bone requires a pedicle graft (with its own blood supply).

The causes of failure of any skin graft may be divided into (a) systemic factors, such as anemia (which is very important in burn grafting), high postoperative fever, hypoproteinemia, etc.; and (b) local factors, such as (i) inadequate hemostasis, (ii) presence of infection, (iii) insufficient or uneven dressing, (iv) inadequate immobilization of the neighbouring joints, (v) poor preparation of the granulating surface. In this regard some interesting work in Kansas has shown that the pH of the granulation tissue may be a valuable index as to when the graft will take—the optimum being about 7.4.

A few uses of split thickness skin grafts will be mentioned just briefly, since most of them are familiar.

(a) The use of grafts in the treatment of burns is a topic of great importance. There are indications for immediate grafting (when the area is small and the burn is third degree), but the most common practice is to wait for two to three weeks until the patient's general condition (e.g., anemia) is improved and there is a bed of healthy granulation tissue. Then grafting is done where necessary for the purpose of preventing deforming scars and contractures. Early skin grafting also helps greatly in preventing secondary infection of the burned area and in improving the patient's general condition.

One interesting new application of skin grafting in the treatment of burns has been the use of homografts in very large burns (over 30%), where insufficient autograft skin is available. Grafting is done by an "alternate strip method" in which 1½-inch strips of homograft skin are alternated with ½-inch strips of autograft. The epithelium of the autograft spreads across the dermis of the degenerating homograft, the composite graft functioning to prevent further loss of colloids and hemoconcentration, infection and scarring. Due to relative agammaglobulinemia in burns, some of these homografts survive much longer than expected. This method also serves to conserve autograft skin for important areas such as the face, hands and flexor surface of joints which are always grafted as soon as possible.

Other common uses of autogenous skin grafts are in cases of (b) mechanical trauma, especially common in the digits, (c) in the surgical repair of wounds such as in mastectomy or in surgery of the face, (d) to speed the healing of a varicose ulcer. More unusual uses which have been tried are (e) in the reconstruction of the esophagus and the urethra.

Dermis, without epidermis, has also been used for various purposes, the most notable being repair of dura and hernial defects. There has also been some recent work in Cleveland using dermis for

plastic reconstruction of the common bile duct, but this has not met with much success yet. Many surgeons feel that it has no advantage over fascia and is more difficult to obtain.

Finally we come to the other type of epithelium, namely glandular. Endocrine glands, like skin and kidney, are homovital grafts—that is, the cells must survive and function if the graft is to fulfill its purpose. The transplantation of various glands is one of the newest and most interesting uses of tissue transplants but has very few clinical applications as yet.

Several principles must be kept in mind: (a) autografts (or homografts) survive only if they are placed in a suitable vascular site (such as in muscle), and cut in thin slices to permit the development of a blood supply; (b) there is a debate about whether the host must be deficient in order for any endocrine transplant to succeed, but this is probably only true in the case of gonads which seem to require the trophic hormones of the pituitary; (c) almost all the clinical successes with homografts have been with foetal endocrine glands, due presumably to their lack of specificity, and this makes a supply of transplants very difficult to obtain; (d) if there is a reasonable chance of the graft succeeding, the operation of transplantation is relatively easy and harmless.

Several examples only will be mentioned of endocrine transplants: (a) Gaillard's transplantation of neonatal parathyroid tissue to cases of post-operative tetany, about one third of which succeeded in the younger age group. (b) Jones of London reports a case of intractable menopausal symptoms which responded to the transplanting of fresh chopped up foetal ovaries to the rectus muscle. (c) Some transplants of chopped up testis tissue have restored the secondary sex characteristics to criminals castrated in penitentiary.

D. Summary and Conclusion

The fundamental concepts and definitions necessary for an understanding of free tissue transplants have been presented. In the case of each tissue, an attempt has been made to relate the basic structure and function to the possible clinical applications. It is hoped that this article will have at least succeeded in arousing the reader's interest in the vast field of tissue transplantation.

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NAUSEA AND VOMITING: MECHANISM AND TREATMENT

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NAUSEA and vomiting occur as manifestations of many organic and psychiatric disturbances. Nausea may occur alone or it may precede a vomiting attack. The severity of a vomiting attack varies according to the cause. The more severe attacks can be most distressing to the patient, leading to fatigue, weakness, malnutrition, electrolyte disorders and eventually to circulatory collapse and death. Control of nausea and vomiting therefore, often becomes the primary aspect of therapy superseding temporarily the treatment of the primary disease. Active treatment of the primary disorder is undertaken when fluid-electrolyte disturbances and shock have been controlled.

DEFINITION:

Vomiting has been defined by Borison and Wang[1] as the forceful expulsion of gastro-intestinal contents through the mouth. Nausea is a psychic experience of human beings which may not be associated with vomiting. It is difficult to describe but easily recognized.

MECHANISM:

Vomiting is a complex syndrome involving the co-ordinated action of many structures. The muscles of respiration play a more important role than do those of the gastro-intestinal tract. It has been shown that during vomiting the stomach appears as a flaccid bag with the cardia relaxed. A sharp contraction of the diaphragm and abdominal muscles compresses the stomach and is followed by the ejection of gastric contents through the cardia into the oesophagus. A deep contracture at the incisura angularis offers an effectual barrier to the passage of stomach contents in a downward direction. The oesophagus remains relaxed throughout, the glottis remains closed, the larynx and hyoid bone are drawn upward and forward and are held rigidly in position. Respirations are inhibited and the naso-pharynx is blocked off by the elevation of the soft palate.

The stomach is subject to similarly strong compressive forces during coughing and defecation as occur in vomiting, but expulsion of gastric contents does not occur possibly as a result of increased tone of the cardiac sphincter. Although the stomach plays a passive role in the vomiting process per se, reverse peristalsis plays a major role in the vomiting of bile and fecal-stained material in intestinal obstruction[2].

Little is known about the mechanism of nausea. It is coincident with loss of gastric tone.

In addition to the complex muscular activity involved in vomiting, there usually occur associated phenomena such as salivation, forced inspiration, vasomotor changes, psychic changes, and a characteristic posture.[1] This syndrome led to the postulation of a vomiting center to control and co-ordinate in proper sequence the various components of vomiting. The recent work of Borison and Wang has done much to clarify the nature of the center.

The vomiting center is located in the medulla and consists of two parts, a "deep" and a "superficial". The "deep vomiting center" is located at the dorso-lateral border of the lateral reticular formation. The function of this center is to co-ordinate the activities of other neural structures in its immediate vicinity in order to produce the complicated patterned response of vomiting .This is in keeping with the general concept of a "center". No "center" has as its sole function the complete regulation of any

single activity; rather the neurons of the center, among their diverse functions, can act together and be instrumental in co-ordinating a given response.

The superficially located "chemoreceptor trigger zone" (CTZ) is sensitive to drugs and other agents carried by the blood stream. On stimulation, the CTZ sends impulses via its efferent fibers to the "deep vomiting center" which in turn sets into motion the vomiting response. The "deep vomiting center" is stimulated also by a second afferent pathway carrying impulses from anywhere in the body, via cranial, somatic and autonomic afferent fibers. It is also postulated that as yet unknown supramedullary receptors and pathways may initiate vomiting and influence the excitability of the "deep vomiting center". Psychic influences may cause vomiting via this postulated pathway.

In summary, the act of vomiting is always mediated by the same "final common path" whose origin is the "deep vomiting center". The latter is stimulated indirectly by circulating chemicals via the superficial CTZ and directly by nervous afferents from anywhere in the body. [3, 4, 5]

CLASSIFICATION:

Vomiting is a very common manifestation of bodily dysfunction and often of unknown origin so that a complete classification is very difficult. The one presented here is based primarily on mechanism of vomiting.[6, 7] "Central vomiting" is due to direct stimulation of the medullary centers (deep or superficial), while "peripheral vomiting" is due to stimulation of the "deep vomiting center" by sensory afferent fibers.

A. PERIPHERAL VOMITING (Reflex vomiting).

1. *Olfactory nerve*: offensive smells.
2. *Optic nerve*: repulsive sights.
3. *Vestibular nerve*: labyrinthine stimulation, e.g.: motion sickness, Meniere's disease.
4. *Glossopharyngeal and vagus nerves*:

   (a) Gastrointestinal.

      i. Gastric:
      Physical: irritating foods.
      Chemical: poisons, intragastric copper sulphate.
      Mechanical: obstruction, portal hypertension (venous congestion).
      Inflammatory: gastritis, peptic ulceration.
      Neoplastic: usually malignant, either obstructive or non-obstructive.

      ii. Intestinal, peritoneal and visceral:
      Physical and chemical factors.
      Mechanical: obstruction, portal hypertension.
      Inflammatory: gastroenteritides, appendicitis, peritonitis, cholecystitis, pancreatitis.
      Colic: renal and biliary.
      Female pelvic conditions: extrauterine gestation, ovarian disease, pregnancy.

   (b) Respiratory: irritation of fauces, pharynx, larynx, bronchi and lungs by direct stimulation or by severe coughing.

   (c) Cardiovascular: myocardial infarction, pericarditis.

5. *Pain*: from anywhere in body.

B. CENTRAL VOMITING

1. *Brain and Meninges.*

   (a) Traumatic: concussion, etc.

   (b) Inflammatory: abscess, encephalitis, meningitis.

(c) Cerebrovascular accident: haemorrhage, embolus, thrombus.
(d) Neoplasm.
(e) Increased intracranial pressure from any cause (vomiting usually projectile and not preceded by nausea).
(f) Epilepsy, migraine.

2. *Cerebellar disturbances.*
3. *Psychic disturbances.*
4. *Metabolic*: uremia, diabetic coma, hepatic coma; Addison's disease.
5. *Drug toxicity*: tobacco, anesthetic, digitalis, morphine, apomorphine, etc.
6. *Toxins* (exogenous and endogenous).

TREATMENT.

The treatment of nausea and vomiting varies with the severity of the vomiting. In those cases where vomiting is of short duration and/or mild, no supportive therapy is required. In severe cases the treatment of the patient as a whole temporarily takes precedence over the treatment of the primary lesion. If the cause of the primary lesion is not known, a comprehensive programme of treatment must be undertaken with a view to supporting the patient until the lesion corrects itself. The following general plan of treatment is presented bearing in mind that it must be flexible, depending on the individual patient.[8]

1. Bed rest.
2. Analgesia and sedation.
3. Restoration of blood loss.
4. Restoration of fluid balance. When severely dehydrated, a hemoglobin determination at hourly intervals may be a valuable index of hydration.
5. Restoration of electrolyte balance. Routine laboratory analyses supply valuable indices, e.g. plasma electrolytes, non protein nitrogen, and carbon dioxide combining power; urine volume and specific gravity.
6. Gastric or duodenal drainage.
7. Gastric lavage.
8. Oral feedings are stopped temporarily.
9. Antiemetic agent.

The specific treatment of vomiting with antiemetic agents is indicated in certain well-defined instances. Treatment may be undertaken in those cases where the administration of the anti-emetic agent in no way interferes with the general condition of the patient and this therapy in no way aggravates a local or general malady. Where a severe illness is present, the onset of vomiting with its inevitable sequelae may endanger the life of the patient. In such a situation, carefully chosen antiemetic agents may be indispensable. When vomiting is due to any condition against which rapid and efficient treatment is available (e.g.: appendicitis), the use of antiemetic agents is unnecessary.

The symptoms and signs which accompany most clinical conditions in which nausea precedes vomiting include anorexia, drowsiness, malaise, headache, fatigue, mental depression, pallor, cold sweat and salivation. There is, however, great variation in the clinical picture from case to case. Since many of the above signs and symptoms are similar to those evoked by acetylcholine or by the nervous system, parasympatholytic drugs were among the first drugs tried therapeutically. The belladonna alkaloids were first used in the late 19th century in the treatment of motion sickness, atropine being the prototype.

Vitamins have been used in the treatment of nausea and vomiting of pregnancy, radiation sickness, Meniere's disease and other causes.

The introduction of the antihistaminic

Source of Emesis	Recommended Agent	Dose (mg,)*	Common Side Effects
Drug Induced			
Opiates	Bonamine	25–50 bid	Somnolence, and sedation. (very low incidence)
	Marezine	50 tid	Somnolence (high incidence).
	Dramamine	100 qid	Somnolence and sedation in 50% of patients.
Digitalis	Thorazine	10–25 qid	Drowsiness. Potentiating narcotics and analgesics. Severe hypotension. Acts like a local anesthetic on direct application to mucous membrane.
Nitrogen Mustard	Thorazine	25–50 qid	
Alcoholic state	Thorazine	50–150 qid	
Infections and Toxicoses	Thorazine	10–25 qid †	
Post-Operative Vomiting			
prophylactic	Dramamine	50 tid-qid.	
	Benadryl	50–100 tid-qid	
	Marezine	50 tid	
therapeutically	Thorazine	25–50 tid	
Pregnancy	Bonamine (with or without pyridoxine)	25–50 h.s.	
Motion Sickness			
airsickness	Scopolamine or Bonamine	0.65-1.0 25.0 bid	Dry mouth and mental depression.
seasickness	Bonamine	50.0 q.d.	

* Refers to oral dose.
q.d. —once per day
b.i.d. —twice per day
t.i.d. —three times per day
q.i.d. —four times per day
h.s. —bedtime
† —may increase dose to 50 mg. if necessary to arrest vomiting.

compounds in the treatment of nausea and vomiting was a major advance. In 1945 diphenhydramine (Benadryl) was found to have antiemetic properties. Since then many antiemetics have been produced, e.g.: dimenhydrinate (Dramamine), meclizine (Bonamine), cyclizine (Marezine), chlorpromazine (Thorazine) and promethazine (Phenergan).

In the above table is a therapeutic classification of emesis and the recommended antiemetic agent is presented.[5, 9]

SIDE EFFECTS OF ANTIEMETIC AGENTS:

Side effects are usually mild but occur in 20 to 75% of patients. The severity and frequency are proportional to the dose and depend on the antiemetic agent. These effects are sedation, dizziness, dry mouth, weakness, fatigue, blurring of vision, insomnia, nervousness, constipation and diarrhoea. The most important immediate side effect associated with Thorazine is a sudden drop in blood pressure following either oral or paren-

teral administration. It is impossible to predict which patient will manifest the hypotensive effect; in any patient, it is undesirable. A rest period of 30 to 40 minutes following every administration of Thorazine should be allowed. More serious long-term side effects, such as hepatic dysfunction and jaundice are more common with the prolonged use of the drug in large doses as is the practice in psychiatric conditions. Agranulocytosis may occur within a shorter period of time and consequently serial white blood counts should be done routinely.

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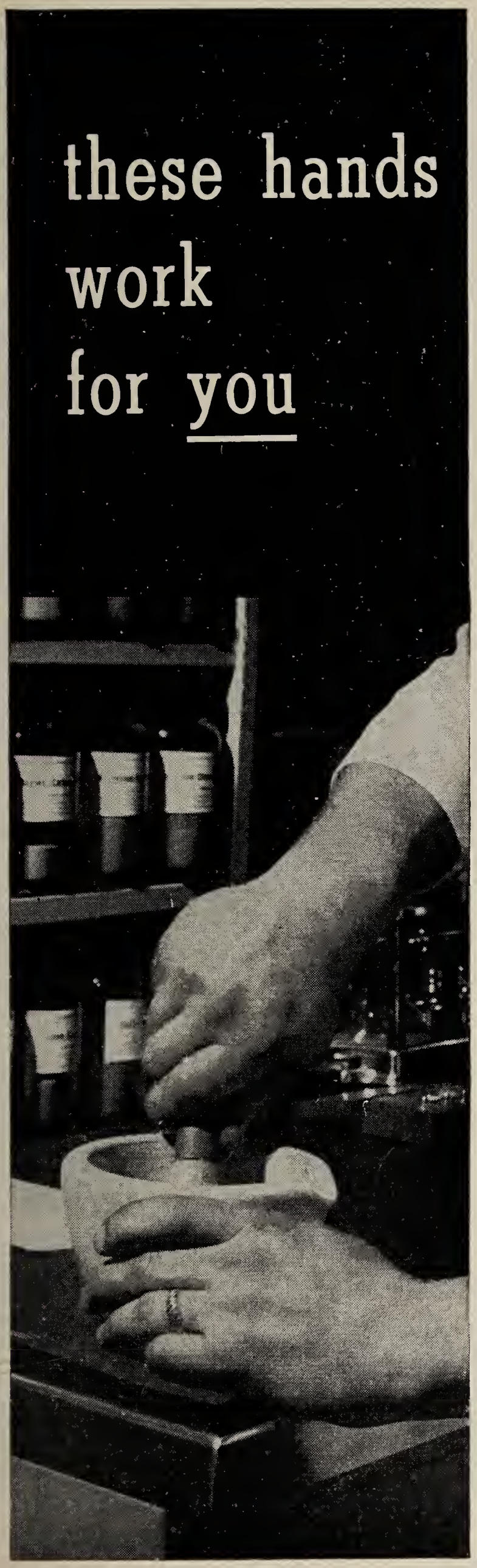

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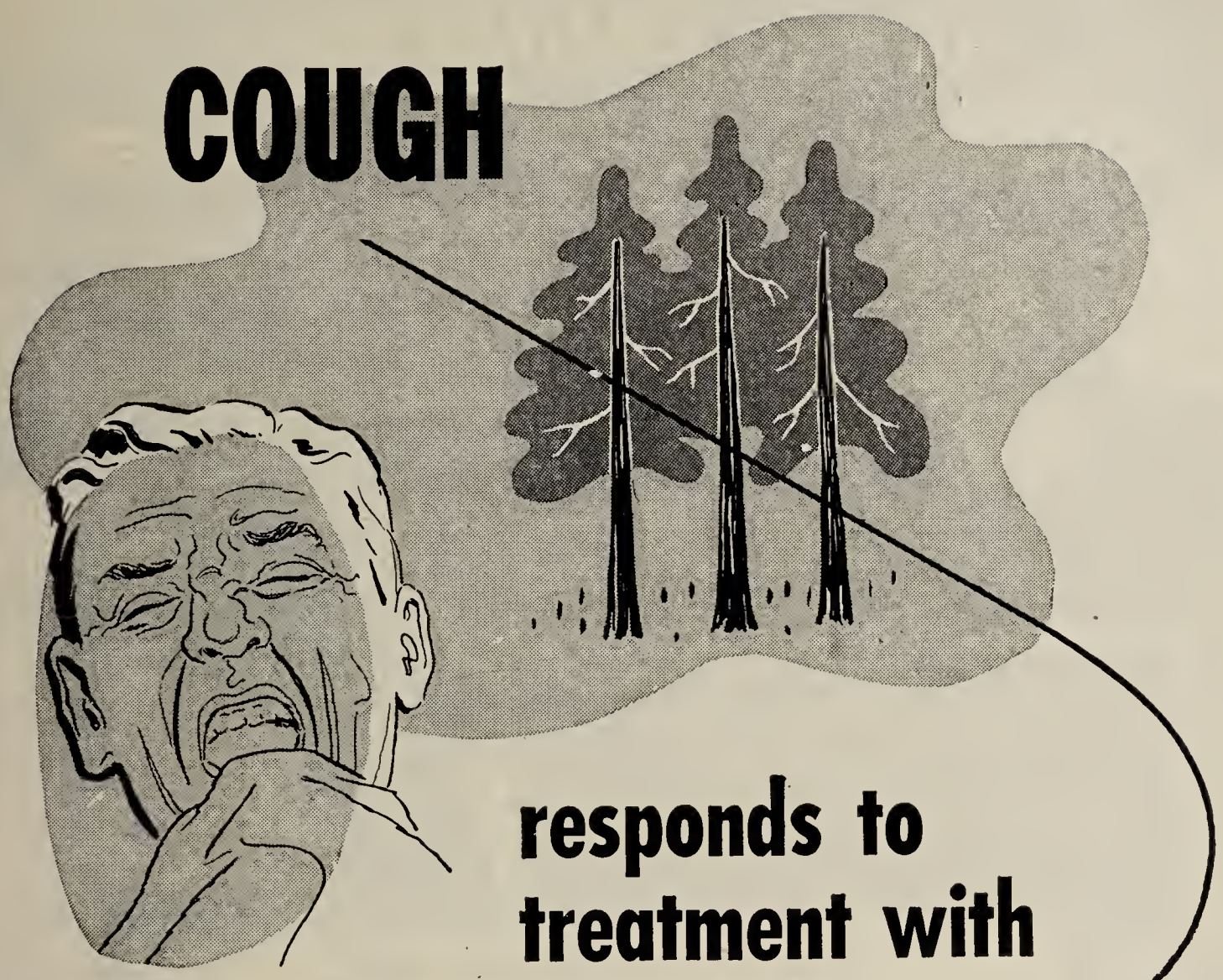

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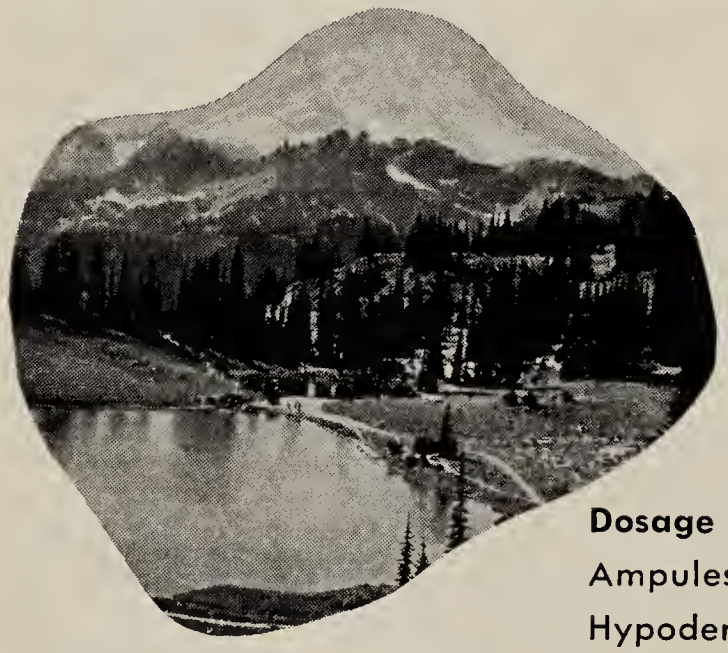

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Hypodermic Tablets: 2 and 4 mg. each.

Oral Tablets: 2.7 mg. each.

Multiple Dose Vial: 10 cc., 2 mg. Dilaudid sulfate per cc.

Dilaudid, Trademark reg., marketed by Knoll Pharmaceutical Company, Orange, N. J.

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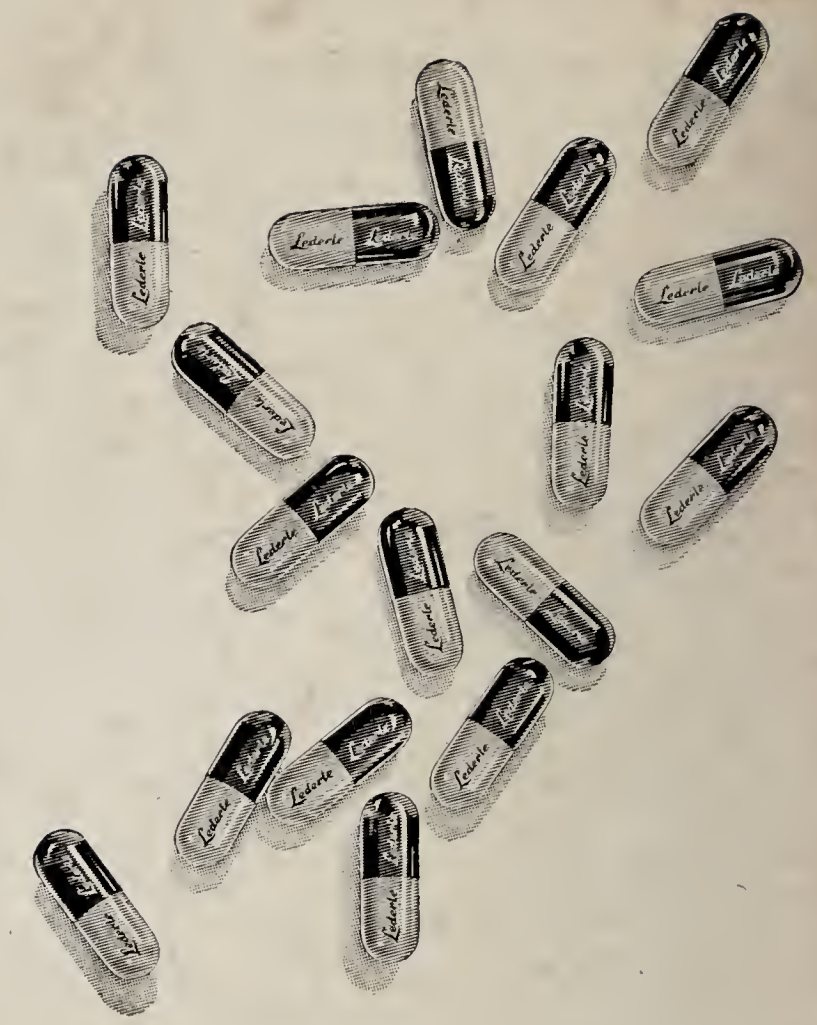

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